Brief Scientific Abstract: Clinical Protocol for Modification of Tumor Suppressor Gene Expression in Head and Neck Squamous Cell Carcinoma (HNSCC) with an Adenovirus Vector Expressing Wildtype *p53*

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OBJECTIVES

1) To determine the maximum tolerated dose of the wild-type p53 adenovirus vector in patients with refractory HNSCC.

2) To determine the qualitative and quantitative toxicity and reversibility of toxicity of this treatment approach.

3) To document observed antitumor activity of this treatment approach.

BACKGROUND AND RATIONALE

Head and Neck Squamous Cell Carcinoma mortality remains at nearly 50% and has not significantly changed since contemporary radiation therapy was implemented over thirty years ago. Local/regional control remains a major issue in this patient population with only approximately 10% of patients with advanced disease succumbing to distant disease alone. The goal of this research is to directly modify the cancer cell to express large quantities of exogenously introduced wild-type p53 tumor suppressor gene product that suppresses the characteristics of the malignant phenotype with no long-term effect upon non-malignant tissues or the cancer patient.

PATIENT ELIGIBILITY (Critical inclusion criteria listed only)

1 Patients must have histologic proof of squamous cell carcinoma of the head and neck. Patients must be either unable to receive conventional treatment (e.g. the patient received radiation therapy with or without surgery) or have failed conventional treatment. Those patients with extensive local or regional disease that have persisted or recurred following radiation therapy (with or without chemotherapy or surgery) and have clinically resectable, but likely non-curable (<10% disease free survival) are also eligible. Patients need not have received a trial of chemotherapy prior to entering this protocol. All eligible patients will be discussed at the Head and Neck Surgery Multidisciplinary Treatment Planning Conference prior to protocol enlistment.

2 Patients must have clinical evidence of advanced local and/or regional cancer which is unresectable or for which no meaningful resection with surgical margins will be obtainable.

TREATMENT PLAN

1 The study will be an open-label upward dose ranging study for adenovirus-*p53* vector (Ad5CMV-p53). Two study patient groups will consist of a) resectable and b) non-resectable recurrent disease. It is not known what toxicities if any will be caused by the adenovirus. The first phase of the study will allow assessment of toxicities related only to the vector. Patients will receive one intratumor injection of Ad5CMV-p53. The initial dose will be 10^6 plaque forming units (PFU). Three patients will be entered at each dose level with 6 patients entered at the maximum tolerated or maximum attainable dose (limitation imposed by production of the adenovirus). Dose escalation is described within the enclosed protocol.

2 Patients with local-regional tumors will have injection of a total dose of 10 ml for tumors $\geq$ 4 cm in diameter or 3 ml for tumors < 4 cm in diameter of the adenovirus preparation with the appropriate number of viral particles at multiple sites percutaneously or transorally. Injections will be placed at approximately 1 cm increments.

3 The treatment will be repeated 3 times weekly for 2 weeks. Treatment will continue on a monthly basis as long if there is no tumor progression. After one year the patients will be evaluated for continuation of therapy.

4 Those patients with surgically resectable disease will be treated by tumoral injection of adenovirus preparation as described in 2 and 3. The treatment will be repeated for 2 consecutive courses. Within 4 days of completion of the 2nd course, the patients will be eligible to proceed with surgical resection. At the completion of surgical resection, prior to closure, 10ml of adenovirus preparation will be administered into the surgical defect (operative bed) and allowed to remain in contact for 60 minutes. The wounds are then closed and drains placed. Post-operatively, on the 3rd post-operative day (prior to drain removal), 10ml of adenovirus preparation is sterilely intro-duced into the drains and retrograde placed into the wounds and allowed to remain for 2 hours. The drains are then replaced to suction and removed when indicated by the attending staff surgeon.